Journal of Advances in Medicine and Medical Research

33(22): 24-30, 2021; Article no.JAMMR.75164
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

The Preferred Premedication Order to Prevent Infusion Reactions in Patients with Breast Cancer Receiving Pertuzumab Plus Trastuzumab and Docetaxel

Shigeru Nakagaki [a], Ryoichi Matsunuma [b*], Kei Yamaguchi [b], Ryosuke Hayami [b] and Michiko Tsuneizumi [b]

[a] Department of Pharmacy, Shizuoka Prefectural Hospital Organization, Shizuoka General Hospital, Shizuoka 420-8527, Japan.
[b] Department of Breast Surgery, Shizuoka Prefectural Hospital Organization, Shizuoka General Hospital, Shizuoka 420-8527, Japan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i2231156
Editor(s):
(1) Chan-Min Liu, Xuzhou Normal University, China.
(2) Rameshwari Thakur, Muzaffarnagar Medical College, India.
Reviewers:
(1) Lee Wai Peng, Changi General Hospital, Singapore.
(2) Khaled Omran, University of Tobruk, Libya.
Complete Peer review History: https://www.sdiarticle4.com/review-history/75164

Original Research Article

Received 27 August 2021
Accepted 07 November 2021
Published 10 November 2021

ABSTRACT

Aims: Pertuzumab plus trastuzumab and docetaxel is a standard regimen for human epidermal growth factor receptor 2 (HER2)-positive breast cancer in the metastatic, adjuvant, and neoadjuvant settings. Infusion reaction represents one of the common side effects of anti-HER2 agents. There is no standard premedication to prevent infusion reactions, although antihistamines, acetaminophen, and/or corticosteroids are often used for this purpose. This study evaluated the ability of premedication to prevent induction reactions in patients receiving pertuzumab, trastuzumab, and docetaxel.
Methods: This retrospective, single-institute study assessed infusion reactions in 72 women with HER2-positive early breast cancer who received pertuzumab, trastuzumab, and docetaxel between

**Corresponding author: E-mail: r-matsunuma@nifty.com;*

November 2018 and April 2021. Thirty-six patients received premedication consisting of oral acetaminophen prior to pertuzumab and trastuzumab administration and dexamethasone and D-chlorpheniramine maleate intravenously prior to docetaxel administration (previous regimen). Thirty-six patients received premedication consisting of acetaminophen, dexamethasone, and D-chlorpheniramine maleate sequentially prior to pertuzumab, trastuzumab, and docetaxel administration (current regimen).

Results: The rates of infusion reaction after the initial injection were 55.6 and 16.7% in the previous and current regiment groups, respectively (p = 0.001). Trastuzumab more frequently caused infusion reactions than pertuzumab and docetaxel. Chills, vomiting, and nausea were the major symptoms of infusion reactions.

Conclusion: Premedication featuring the upfront use of dexamethasone and D-chlorpheniramine maleate prior to the administration of anti-HER2 targeted agents significantly prevented infusion reactions.

Keywords: Pertuzumab; Trastuzumab; Infusion reaction; Premedication; Prophylaxis.

1. INTRODUCTION

Trastuzumab, an antihuman epidermal growth factor receptor 2 (HER2) monoclonal antibody, significantly improves outcomes among patients with HER2-positive breast cancer when used together with chemotherapy compared to the effects of chemotherapy alone [1,2]. Trastuzumab binds to subdomain IV of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2 cleavage [3], stimulating antibody-dependent, cell-mediated cytotoxicity [4], and inhibiting ligand-independent, HER2-mediated mitogenic signaling [5]. Pertuzumab is a humanized anti-HER2 monoclonal antibody that has complementary mechanisms of action to trastuzumab based on their binding to different domains [3,4]. Specifically, trastuzumab binds close to the transmembrane domain, inhibiting HER2 dimerization, whereas pertuzumab binds to the dimerization domain, inhibiting HER2 heterodimerization with other HER family receptors. Both antibodies activate antibody-dependent cellular cytotoxicity. Dual HER2 blockade with pertuzumab and trastuzumab is the standard of care for patients with HER2-positive malignancy. One of the standard regimens for HER2-positive breast cancer is pertuzumab plus trastuzumab and docetaxel in the metastatic, adjuvant, and neoadjuvant settings [6-8].

Although monoclonal antibodies such as pertuzumab and trastuzumab are better tolerated with less toxicity than cytotoxic agents, they often cause infusion reactions [9,10]. Infusion reactions typically arise after the first or second infusion, and they are typified by a variety of symptoms including chills, fever, nausea, asthenia, headache, skin rash, and pruritus [9]. Whereas premedication with antihistamines, acetaminophen, and/or corticosteroids is commonly used to prevent infusion reactions following monoclonal antibody administration, the efficacy of premedication agents has not been sufficient studied and compared. Thus, this study evaluated the ability of premedication to prevent infusion reactions following treatment with pertuzumab, trastuzumab, and docetaxel.

2. PATIENTS AND METHODS

This study enrolled patients with HER2-positive breast cancer who were treated with pertuzumab plus trastuzumab and docetaxel in the adjuvant or neoadjuvant setting (n = 72) at Shizuoka General Hospital in Japan between November 2018 and April 2021. Patients received a fixed loading dose of 840 mg of pertuzumab in the first cycle. Trastuzumab (Herceptin ®) was given at a loading dose of 8 mg/kg body weight in the first cycle. Docetaxel was administered at a dose of 75 mg/m2. From November 2018 to October 2019, 36 patients received premedication featuring 400 mg of oral acetaminophen prior to the administration of pertuzumab and trastuzumab followed by 6.6 mg of intravenous dexamethasone and 5 mg of intravenous D-chlorpheniramine maleate prior to the administration of docetaxel (previous regimen). From November 2019 to April 2021, 36 patients received premedication with 400 mg of oral acetaminophen, 6.6 mg of intravenous dexamethasone, and 5 mg of intravenous D-chlorpheniramine maleate prior to pertuzumab, trastuzumab, and docetaxel administration (Fig. 1). When the number of patients for current regimen reached 36 in April 2021, analysis was performed. The incidence of infusion reactions after the start of administration of pertuzumab was studied retrospectively.

Patients' demographic and tumor characteristics were collected from the electronic medical record. Infusion reactions were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. All statistical tests were two-sided, and p-values < 0.05 were considered significant.

3. RESULTS

The ages of the patients in the previous and current regimen groups ranged 31–75 (mean, 54.6 years) and 35–79 years (mean, 56.2 years), respectively. There was no significant difference in the mean body mass index between the previous and current regimen groups (22.2 kg/m2 vs. 23.8 kg/m2, p = 0.113). Although clinical stage and the Ki67 level were well balanced in both groups, the rate of estrogen receptor and/or progesterone receptor positivity was numerically higher in the current regimen group (50.0% vs. 72.2%, p = 0.053). Meanwhile, 94.4% of patients in the previous regimen group received prior chemotherapy, versus 91.7% of those in the current regimen group (p = 0.546). The proportion of patients with drug allergies did not differ between the groups (p = 0.609), nor did eosinophil counts (p = 0.645, Table 1).

In total, 55.6% (grade 1, 38.9%; grade 2, 16.7%) of patients in the previous regimen group experienced infusion reactions in the initial cycle, versus 16.7% (grade 1, 11.1%; grade 2, 5.56%) of patients in the current regimen group (p = 0.001, Fig. 2A). No patients exhibited grade 3 or higher reactions. In the second cycle, only one patient in the previous regimen group experienced infusion reactions. Concerning the causative agent, 80.0 and 66.7% of infusion reactions in the previous and current regimen groups, respectively, occurred during trastuzumab treatment (Fig. 2B). Chills represented the most common symptom of infusion reactions, followed by vomiting and nausea. Fever, headache, pruritus, and muscular pain occurred in relatively few patients (Table 2).

Table 1. Patient characteristics

	Previous premedication	Current premedication	*p*-value
Age			0.54719
Mean ± SD	54.6 ± 11.7	56.2 ± 10.5	
Body Weight (kg)			0.13521
Mean ± SD	55.0 ± 8.7	59.0 ± 13.0	
Body Mass Index (kg/m2)			0.11323
Mean ± SD	22.2 ± 3.1	23.8 ± 5.1	
Stage			0.95833
Ⅰ	6	11	
Ⅱ	19	20	
Ⅲ	11	4	
ER and/or PgR			0.05312
Positive	18	26	
Negative	18	10	
Ki67			0.96252
0-30	14	22	
31-60	16	11	
61-100	6	2	
Prior chemotherapy			0.54649
Yes	34	33	
No	2	3	
Setting			0.70031
Adjuvant	9	10	
Neoadjuvant	27	26	
Drug Allergy			0.60887
Yes	10	12	
No	26	24	
Eosinophil Count			0.64476
Mean ± SD	49.3 ± 53.1	44.1 ± 40.1	

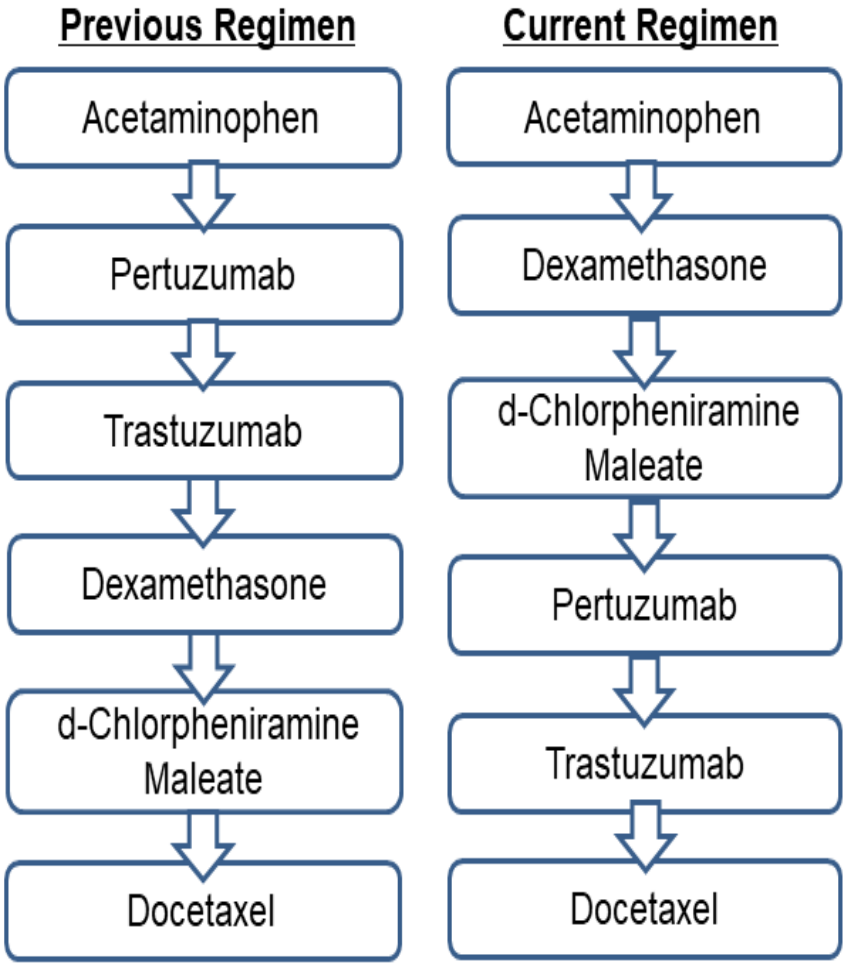

Fig. 1. Previous and current regimens of premedication for pertuzumab plus trastuzumab and docetaxel are presented

Table 2. Infusion reaction symptoms

	Previous Premedication (No. of Patients)	Current Premedication (No. of Patients)
Chills	13	2
Vomiting	10	1
Nausea	5	0
Flushing	3	3
Dyspnea	3	0
Fever	2	0
Headache	2	0
Pruritus	1	0
Muscular pain	0	1
Discontinuation in the cycle	2	1

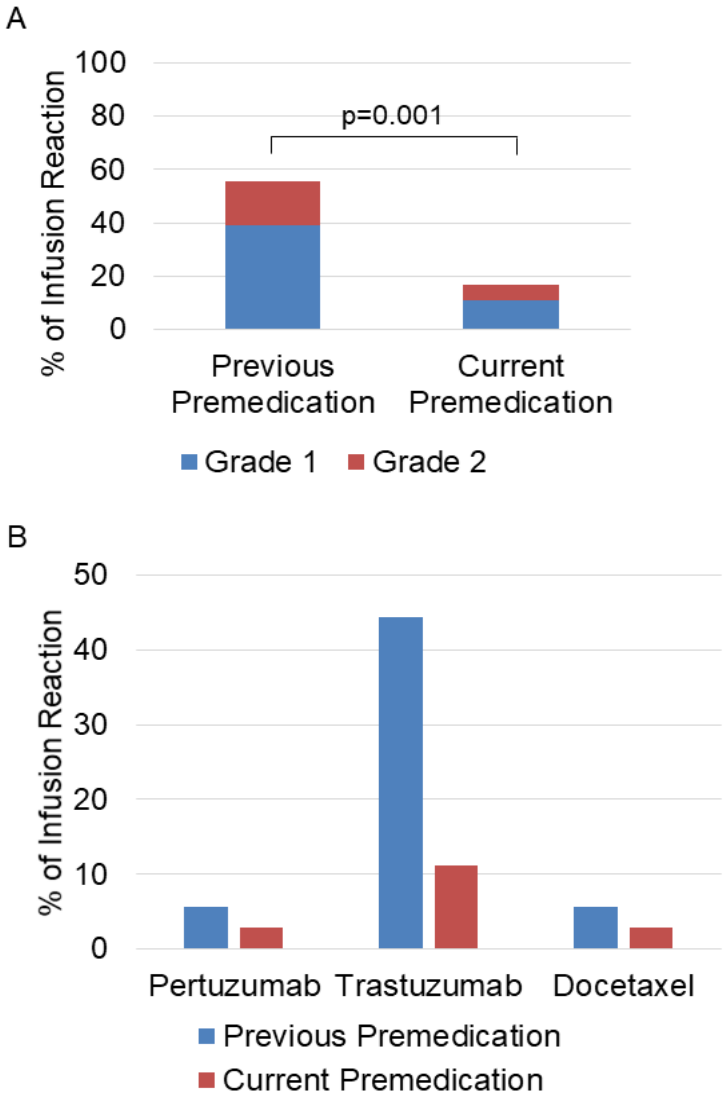

Fig. 2. Comparison of infusion reaction rates. (A) Bar graph depicting the incidence of infusion reactions in the previous and current premedication groups. p-values were derived using Fisher's exact test. (B) Bar graph depicting the incidence of infusion reaction during pertuzumab, trastuzumab, and docetaxel administration in the previous and current premedication groups

4. DISCUSSION

Anti-HER2 targeted therapies such as pertuzumab and trastuzumab improved outcomes among patients with HER2-positive breast cancer in the adjuvant, neoadjuvant, and metastatic settings [6-8]. The rate of infusion reactions during trastuzumab treatment in patients who did receive premedication ranged 13–40% in prior research [11,6,8]. Some surveillance data identified "pulmonary toxicity" and "anaphylaxis" as rare but potentially life-threatening reactions associated with less than 1% of trastuzumab infusions [12,13]. Patients who had infusion reactions required dose interruptions, extending their chair time in the infusion center and potentially delaying other patients from receiving their scheduled treatments [10]. It is pivotal to prevent infusion reactions during the initial administration of anti-

HER2 targeted agents because the initial dose of the anti-HER2 targeted agents is more likely to be associated with infusion reactions. Although the European Society for Medical Oncology guideline mentions that premedication is not recommended to prevent trastuzumab-induced infusion reactions, this document is based on retrospective cohort studies or case-control studies, whereas a variety of prophylaxes are used in the clinical practice [14]. In this study, premedication with acetaminophen, dexamethasone, and D-chlorpheniramine maleate prior to anti-HER2 targeted therapy decreased the rate of infusion reactions to approximately one-third of that achieved with premedication using acetaminophen alone prior to anti-HER2 targeted therapy. Almost all events occurred during administration of the anti-HER2 targeted agents. In addition, trastuzumab was more likely to induce infusion reactions than pertuzumab even though both drugs are anti-HER2 targeted agents.

Infusion reactions represent one type of adverse drug reactions (ADRs), which are defined by the United States Food and Drug Administration as 'any undesirable experience associated with the use of a medical product in a patient.' An ADR may be classified as follows: Type A, augmented pharmacological effects; Type B, bizarre; Type C, chronic effects; Type D, delayed effects; Type E, end-of-treatment effects; Type F, failure of therapy; and Type G, genetic reactions.

Infusion reactions are "Type B" reactions, as they are non-dose–related, unpredictable, and generally unrelated to the drug's pharmacological activity and they usually resolve when treatment is terminated. These reactions are divided into true allergic responses (immune-mediated, such as anaphylactic reactions) and non-allergic (non-immune) sensitivities. Type B adverse non-immune reactions include pseudo-allergic (anaphylactoid reactions that resemble true Type I reactions [IgE antibody-mediated reactions] such as cytokine release syndrome), idiosyncratic reactions, and intolerances. Typical signs and symptoms of infusion reactions include flushing, urticaria, pruritus, wheezing, hypotension, nausea, and vomiting. Although the cause of infusion reactions has yet to be elucidated, it is believed that monoclonal antibodies target interactions that can lead to the release of cytokines that produce a range of symptoms similar to those observed in Type I allergic responses [15,14]. Thus, the upfront use of dexamethasone and D-chlorpheniramine maleate prior to the administration of anti-HER2 targeted agents can be effective for inhibiting immune responses induced by drug therapy. Conversely, acetaminophen did not appear to prevent infusion reactions based on the finding that most reactions in the previous regimen group occurred before the administration of dexamethasone and D-chlorpheniramine maleate

This study had significant limitations. The sample size was relatively small, and this was a retrospective study performed at a single institute. Additionally, both dexamethasone and D-chlorpheniramine maleate were chosen in this study, and one of these might be unnecessary for prophylaxis. Therefore, care should be taken when interpreting the results.

5. CONCLUSION

We found that dexamethasone and D-chlorpheniramine maleate significantly inhibited infusion reactions during the initial dose of pertuzumab plus trastuzumab, whereas acetaminophen did not appear to have prophylactic effects.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

The author declares that written informed consent was obtained from all the patients that received pertuzumab, trastuzumab, and docetaxel in this study.

ETHICAL APPROVAL

This study was approved by Shizuoka General Hospital Research Ethical Committee (#2020060) and was conducted in accordance with the Declaration of Helsinki and its later amendments.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/75164